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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/471,523 | 12/23/99 | VAN BREEMEN | R 21726/90386 |

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| EXAMINER | |
|---|---|
| KOROMA, P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1627 | 7 |

**DATE MAILED:** 02/05/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/471,523 | VAN BREEMEN ET AL. | |
| | Examiner | Art Unit | |
| | BARBA M. KOROMA | 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 1999* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

## DETAILED OFFICE ACTION

Receipt is acknowledged of election filed on 11/30/00. Applicant's election of species without traverse in paper No. 6 (11/30/00) is acknowledged.

### *Status of the Claims*

Claims 1-11 are pending in this application.

### *Formalities*

1. In the oath of declaration, the originally inscribed citizenship of inventor, Judy L. Bolton, was crossed out and then replaced with another without due signature authenticating the change. Correction is required.

2. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

3. The specifications are objected to under 37 CFR 1.83(a) for failing to show the drawings referred to in the specifications. The description of Figures 1A, and 1B referred to in the brief description of drawings on pages 4 and 11 do not match the drawings shown. Figures 1A and 1B are missing. Please note that any structural detail that is essential to a proper understanding of the disclosed invention should be shown in the drawings (MPEP § 608.02(d)).

***Claim Rejection 35 USC 112 First paragraph***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors used in determining undue experimentation are as set forth In re Wands, 858 F.2nd 731, 8 USPQ2d 1400 (Fed. Cir 1988) and an undue experimentation analysis. See MPEP §§2164-2164.08(c). The factors to be considered include: quantity of experimentation necessary; the amount of guidance presented; the presence or absence of working examples; the nature of the invention; the state of the prior art; the predictability of the art; and the breadth of claims.

6. Claim 9 recites "ultrafiltration membrane has pore sizes that allow the sample molecules to pass through but not the biological material." However, because the membrane pore size was not specified in standard language such as cm or μm, one skilled in the art would not able to practice the invention. The specifications (page 12, line 14) refer to this size in non-conventional terms, i.e. MWCO (molecular weight cut off).

Using the guidelines set forth In re Wands above, it would require the testing of all the molecules present in a sample in order to first determine individual molecular weights prior to screening them using a membrane based on the molecular weight cut off point as depicted in the specifications. Given the *nature of the art* in which hundreds of molecules in a library are routinely screened, this constitutes an invitation to *undue experimentation* on the part of one skilled in the art to practice the invention.

7. Applicants recite in claim 11 "a kit for analyzing compounds in a sample, said kit comprising in separate containers, an ultrafiltration membrane, a first solution containing a biological material, a buffer, a test solution, and a set of standard solutions with predetermined characteristics." However, no reference was made in the claims or specifications to specific components of the kit.

Under the guidelines set forth In re Wands, this is an invitation to *undue experimentation* because one skilled in the art would have to test several buffers, several reagents, and several proteins of different concentrations as standards, in order to determine what constitutes a test kit assay. Since the *prior art* does not teach how to use make and use this kit, and the claims

*broadly* refer to the make-up of the kit, one skilled in the art would not be able to make and use this kit.

***Claim Rejection 35 USC 112 Second paragraph***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5, 6, 7, 8, 9,10, 11 are rejected under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Applicants recite "a method for determining whether a compound from a sample has *predetermined characteristics*" (claims 1, 6 and 11). However, on page 3, lines 7-10 of the specifications, applicants disclose the predetermined characteristics of a compound as follows: "functioning as substrate for an enzyme in the biological material; showing desirable rates of enzyme catalysis; showing desirable rates of cell membrane permeability or transport; or showing activation to reactive or toxic metabolites." These attributes are not "predetermined" because they were not physically, genetically or biochemically altered or manipulated. Rather, they are referred to as "desired"attributes. Thus, absent a contrary indication, examiner assumes that the said characteristics are merely selected *ex post facto*. Clarification is requested from applicants with respect to "predetermined characteristics."

11. Claim 11 recites "removal of compounds from the sample and their metabolites." This sentence is not clear because it may imply removal of the compounds from their metabolites." Examiner suggests that applicants rephrase the sentence to read "the compounds and their metabolites are removed," if that is line with the intended meaning of the claim language.

12. Claim 6 recites: "showing enzymatic activation to reactive or toxic metabolites." This phrase is ambiguous since the terms 'reactive' and 'toxic' are not synonymous, making it unclear what applicants intend to convey by the concurrent use of both terms. Clarification is required.

13. Claims 1 and 8 recite "the suitable conditions for interaction of biological material in the first solution with the compound in the sample." However, the said conditions were not defined in the specifications (paragraph 3, page 3). Rather, the disclosure reads as follows: the suitable conditions for interaction of the biological material in the first solution with the compound in the sample include "mixing the sample with the biological material to achieve a homogenous distribution, controlling temperature to maintain function of the biological material, providing adequate sample concentration and a sufficient amount of biological material to facilitate analysis, allowing sufficient time for interaction, and controlling time for interaction, and controlling atmospheric gases to maintain function of biological material." Because the claims and specifications do NOT clearly state the temperature, concentration, time, and gas pressure or ratio that make up the suitable conditions, applicants are hereby requested to clarify the meaning of "suitable conditions."

*Claim Rejection 35 USC § 102*

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by **Metzger et al (Ion-Spray mass spectrometry and high performance liquid chromatography-mass spectrometry of synthetic peptide libraries. 1993. *Ang Chem Int Ed Engl.* 32:894-896).** Claim 10 recites "analyzing the second solution by mass spectrometry," and in the specifications pulsed-ultrafiltration mass spectrometry is disclosed (page 2, first paragraph, line 5).

Metzger et al discloses the use of mass spectrometry in analyzing a 48-component peptide mixture (Figures 1-4, pages 895-986). This reference shows that mass spectrometry alone or in combination with HPLC is a valuable tool for estimating the identity, composition, and purity of small and larger peptide mixtures (page 895, last paragraph), which anticipates the claim.

16. Claim10 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by **Stevanovic et al (Natural and synthetic peptide pools: characterization by sequencing and**

**electrospray mass spectrometry. Bioorganic & Medicinal Chemistry Letters. 1993. 3:431-436**).

Stevanovic et al disclose that isolated libraries and their synthetic analogues can be analyzed by electrospray mass spectrometry (see last line, abstract). In pages 3 and 4, this reference also discloses that electrospray and pneumatically assisted electrospray are soft ionization methods in which solute ions are emitted from directly from charged droplets into the gas phase at atmospheric pressure. These techniques are disclosed as especially suited for peptides which form multiply charged quasi-molecular ions (M+nH)n+ (page 434, third paragraph). Stevanovic et al also discloses that the (mass) spectrum allowed an evaluation of the quality of the sub-library because the relative intensities of an ion peak could be correlated with the number of peptides having the particular m/z value. The reference further discloses that electrospray MS (mass spectrometry) could be enhanced by direct coupling of HPLC with the mass spectrometer and the intensity of a peak or the peak area that is correlated to the identical peptides (page 434-435, second paragraph). By disclosing the use of mass spectrometry as described above, this reference anticipates claim 10 of the instant invention.

### *Claim Rejection 35 USC § 103*

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weiboldt et. al. (***Immunoaffinity ultrafiltration with ion spray HPLC/MS for screening small-molecule libraries. 1997. Analytical Chemistry 69:1683-1691).***

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

19. Claim 1 recites "a method for determining whether a compound from a sample has predetermined characteristics,....obtaining a biological solution in a first solution,...maintaining continuous flow through the first solution,...adding the sample to the continuous flow,..... providing suitable conditions for the interaction of the biological material ....with the compound washing the results of the interaction through an ultrafiltration membrane, and analyzing the second solution to determine whether the compound in the sample has the predetermined characteristics".

Weiboldt et. al (1997) discloses a solution-phase screening method of pharmaceutically relevant molecules applicable to screening combinatorial libraries.

20. Specifically, Weinboldt reports the analysis of individual benzodiazepines selected from a multi-component library mixture. The reference discloses the formation in solution of non-covalent immuno-affinity complexes with antibodies raised to therapeutically proven drugs

such as nitrazepam, temazepam, or oxazepam. Captured compounds are separated from nonspecifically bound library components by centrifugal ultra-filtration. The selected molecules retained on the filter are subsequently liberated from antibodies by acidification and analyzed by HPLC coupled with pneumatically assisted electrospray (ion spray) ionization mass spectrometric detection. This procedure selects library components with the greatest affinity for a particular antibody. Specific capture of benzodiazepines is demonstrated by screening both a pool of structurally similar benzodiazepines and a more complex mixture of benzodiazepines with an additional set of unrelated compounds. Weiboldt also discloses that affinity ultrafiltration and electrospray mass spectrometry complement each other to enhance screening and identification of pooled drug candidates. As indicated (underlined), Weinboldt et al's reference bear in common with the instantly-claimed invention a number of essential elements.

The difference between the prior art and the claimed invention of claim 1 is that Weiboldt et al use centrifugal ultrafiltration method for collecting affinity-bound molecules without online mass spectrometric analysis, whereas, in the instant application, an ultrafiltration membrane of a pore size based on the size range of the candidate molecules is used with online mass spectrometric analysis.

The art is replete with uses of both ultrafiltration membranes and centrifugal ultrafiltration, as well as online GC, HPLC, and mass spectrometric analytical approaches in the isolation, purification and analysis of proteins. For example, companies such as BIORAD market centrifugation tubes with built in ultra-filtration membranes for use in purifying proteins. This company also carries high-throughput analytical (GC, HPLC and mass spectrometric) equipment enhanced by computers.

Therefore, it would have been obvious to one skilled in the art at the time the invention was made to use an ultra-filtration membrane to isolate binding complexes in a screening assay, followed by online mass spectrometric analysis as described in the instant application. The motivation stems from the teachings of Weiboldt et al that ultrafiltration enhances screening and identification of drug candidates which can be extended to small-molecule combinatorial libraries.

21. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

22. All inquiries pertaining to this case should be directed to ***Barba M. Koroma.*** This examiner can normally be reached at: **703 305 1915, at *9:00am to 5:00pm, Monday through Friday.***

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, PhD, can be reached at: 703 308 2439. The phone number for the organization where this application or proceeding is assigned is: 703 308 2742. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is: 703 308 1235.

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*Patent Examiner*
AU 1627
January 12, 2001

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